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Summary and Outlook

Isonitrile-Functionalized 3,4-Dihydropyridin-2-ones

Multicomponent Synthesis and Synthetic Potential

Multicomponent reactions (MCRs) have gained considerable popularity in the synthetic community. They combine, in one pot, at least three different easily accessible reagents in a well-defined manner to form a single product by the formation of several new covalent bonds. As such, MCRs are ideal tools for the efficient construction of rather complex molecules. Besides *complexity* generation, *diversity* generation is an important criterion within the concept of diversity-oriented synthesis (DOS). There are three different elements of diversity: (a) appendage diversity, (b) stereochemical diversity, and most importantly (c) scaffold diversity. In order to cover the “chemical space” more effectively, the scaffold diversity in a functional set of target compounds is one of the key issues to overcome, requiring the continuous need for novel reactions. MCRs play an important role in this field of synthetic research.

In the field of multicomponent chemistry the generation of scaffold diversity has often been realized by combining MCRs with several follow-up cyclization reactions resulting in the rapid synthesis of diverse (heterocyclic) scaffolds. However, over the past decade, rational multicomponent design strategies have become much more important, generating scaffold diversity using MCRs exclusively (**Chapter 1**).

Four different approaches are discussed: (i) single reactant replacement (SRR, Figure 1A), (ii) modular reaction sequences (MRS, Figure 1B), (iii) condition-based divergence (CBD, Figure 1C), and (iv) union of multicomponent reactions (MCR², Figure 1D), which all lead to the development of new MCRs and higher order MCRs, thereby addressing both molecular diversity and complexity.

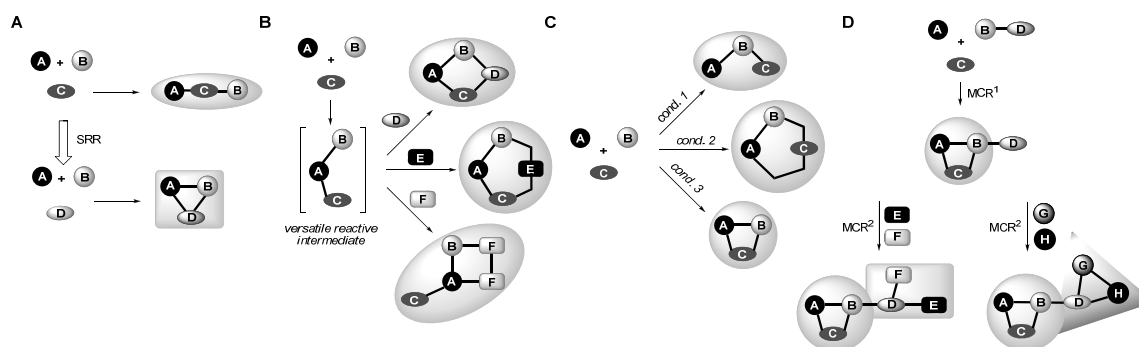
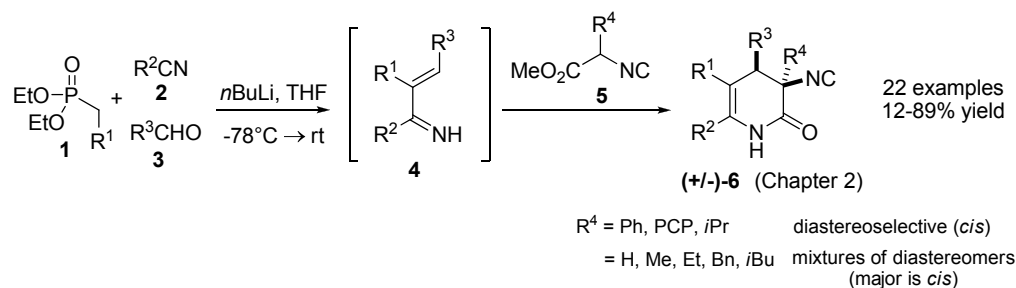


Figure 1. Novel multicomponent design strategies for the generation of scaffold diversity. **A.** Single reactant replacement; **B.** Modular reaction sequences; **C.** Condition-based divergence; **D.** Union of MCRs.

An important part of the work described in this thesis involves MCRs classified under B in Figure 1, *i.e.* the modular reaction sequences (MRS) based on a common intermediate, 1-azadiene **4**, derived from a one-pot reaction of phosphonate **1**, nitrile **2** and aldehyde **3** (Scheme 1). This versatile intermediate can be trapped *in situ* by a fourth component to afford various heterocyclic scaffolds (**Chapter 1**). **Chapter 2** describes an elaboration of this work by the application of isocyanoacetates **5** as the fourth reaction component to arrive at isonitrile-functionalized 3,4-dihydropyridin-2-ones **6** (3,4-DHP-2-ones). In this MCR, the usually rather reactive isocyanide group is retained. Variation of the nitrile (R^2), aldehyde (R^3) and isocyanide (R^4) inputs proved to be extensively possible but variation of the phosphonate (R^1) input is limited.



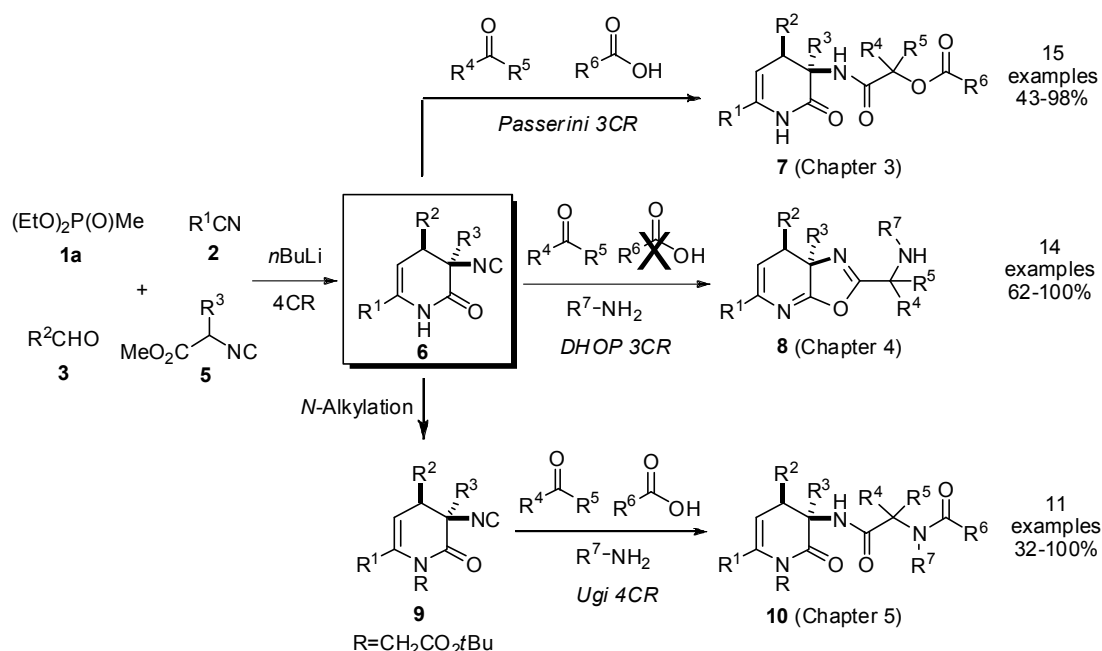
Scheme 1. 4CR leading to isonitrile-functionalized 3,4-DHP-2-one involving a 1-azadiene intermediate.

The use of α -aryl isocyanoacetates ($R^4 = \text{Ar}$) gave the corresponding 3,4-DHP-2-ones in moderate to high yields and with full diastereoselectivity in favor of the 3,4-*cis* isomer. On the other hand, α -alkyl isocyanoacetates ($R^4 = \text{alkyl}$) afforded the corresponding 3,4-DHP-2-ones in moderate yields, commonly as mixtures of diastereomers. Elevated

temperatures during cyclocondensation generally led to an increase in yield and resulted in an improved diastereomeric distribution in favor of the *cis*-diastereomer. Future research will focus on a deeper understanding of reaction mechanism based on experimental and computational findings.

The isocyanide group still present in **6** allows combination of our MCR with a subsequent isonitrile based complexity-generating MCR (the MCR² concept D from Figure 1), as we demonstrate in **Chapter 3** by the (one-pot) combination of the 3,4-DHP-2-one four-component reaction (4CR) with the well-known Passerini 3CR leading to a 6CR for conformationally constrained depsipeptides **7** (Scheme 2). Substituents (appendages) could be independently varied at six different positions.

Surprisingly, reaction of the isonitrile-functionalized 3,4-DHP-2-one with an aldehyde, amine and carboxylic acid (Scheme 2) did not result in the expected Ugi product, but gave the unprecedented dihydrooxazolopyridines **8** (DHOPs), as described in **Chapter 4**. Various DHOPs could be prepared in high yield when the DHP-2-ones are reacted with aldehydes and amines only. The reaction proved to have a high substrate scope and various aldehydes (except paraformaldehyde and benzaldehyde) and amines are applicable.

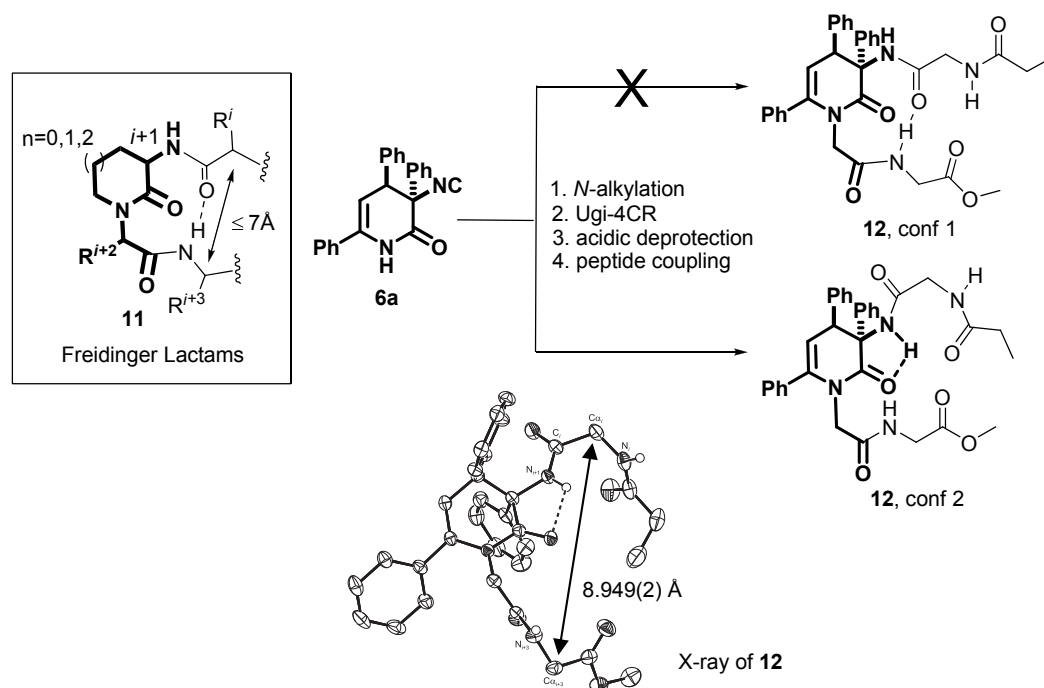


Scheme 2. Follow-up isonitrile-based multicomponent chemistry on the 3,4-DHP-2-one scaffold.

Interestingly, simple *N*-alkylation of the DHP-2-one scaffold **6** (to give **9**, Scheme 2) totally drives the course of the reaction towards the Ugi products **10** (Chapter 5). No limitations were found regarding the three Ugi inputs. In this way highly functionalized conformationally constrained peptide mimics are accessible *via* a method we named the MCR (DHP-2-one 4CR)-alkylation-MCR (Ugi 4CR) strategy.

Overall, three different highly complex products could be prepared from the same 3,4-DHP-2-one scaffold, by applying different successive MCRs, thereby addressing both complexity and diversity generation.

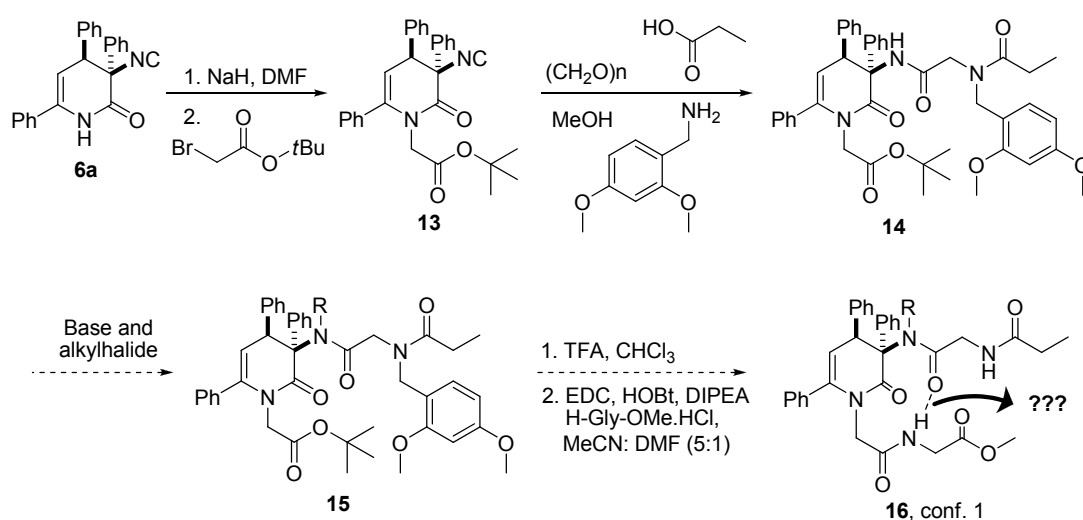
As an application of our new DHP-2-one 4CR we investigated the use of our MCR-based strategies to prepare β -turn mimetics. β -Turns are common structural elements of (bioactive) peptides and proteins and are often essential for their activity. β -Turn mimetics, like the Freidinger lactams **11** (Scheme 3), are conformationally constrained analogues that mimic the β -turn motif of the parent peptide. This may result in an enhanced potency, receptor selectivity and (peptidase) stability. The structural resemblance of the 3,4-DHP-2-one scaffold with the Freidinger lactams inspired us to investigate its potential to function as a turn-inducing moiety (Chapter 5). We prepared the corresponding mimetic by a stepwise procedure: alkylation of the 3,4-DHP-2-one amide *NH* (**6a**) followed by the Ugi-4CR, a *t*Bu deprotection and peptide coupling to afford **12** (Scheme 3).



Scheme 3. Synthesis of constrained peptide **12** from 3,4-DHP-2-one **6a** and its X-ray conformation.

NMR analysis and X-ray diffraction proved that conformation 1 of **12** (possessing an intramolecular hydrogen bond between residues i and $i+3$, forming a pseudo-10-membered ring, like in **11**) was not the actual conformation. The real conformation more resembles conformation 2. This conformation shows an intramolecular hydrogen bond between the carbonyl oxygen of the DHP-2-one ring and the DHP-2-one NH. It is evident from conformation 2 that the 3,4-DHP-2-one scaffold does induce a turn. However, based on the criteria for β -turns (*int. al.* $d(\text{C}\alpha_i\text{-C}\alpha_{i+3}) \leq 7 \text{ \AA}$), compound **12** can not be classified as a true β -turn.

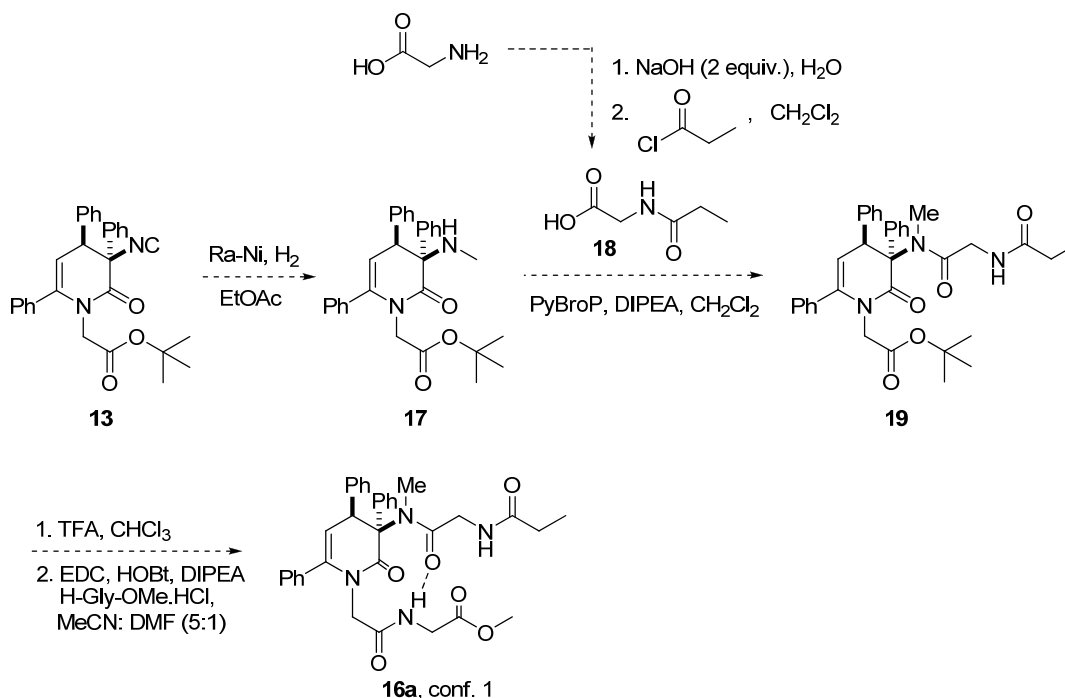
Future research will focus on modifying structure **12** to such an extent that hydrogen bonding between the carbonyl oxygen of the DHP-2-one ring and DHP-2-one NH is not possible anymore, which might result in the formation of a true β -turn (as in conf. 1). One way to achieve this is by preparing the alkylated derivative of **12**, *i.e.* **16**, in which the DHP-2-one NH is alkylated. This might be achieved by alkylation of intermediate **14** to afford **15** (Scheme 4), which is converted into **16** in a similar way as used for **12**. However, due to the comparable pK_a values of the $\text{C}\alpha$ protons of the two glycine residues and the amide NH proton, selective alkylation of the amide NH might not be so easily achieved.



Scheme 4. Synthetic plan for the synthesis of constrained peptide **16** possessing an alkylated 3,4-DHP-2-one NH (NR).

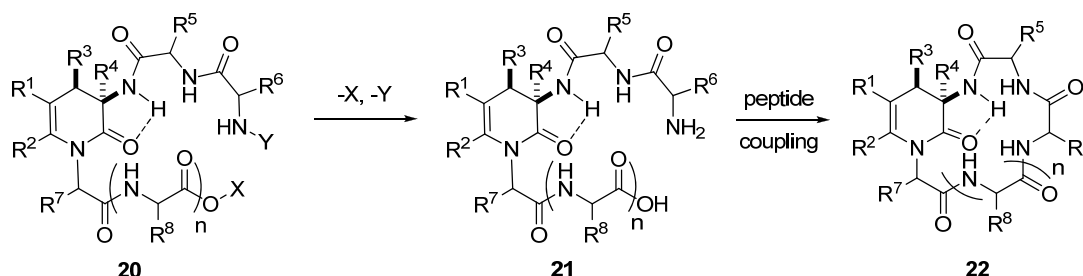
An alternative way is to prepare methylated derivative **16a** (R = Me) by applying a hydrogenation of **13** using Raney nickel, to obtain *N*-methylated amine **17**. Subsequent peptide coupling with propionylglycine **18** (which may be prepared using Schotten-

Baumann conditions starting from glycine) to afford **19**. Finally *t*-Bu removal and peptide coupling with glycine methyl ester can afford compound **16a**.



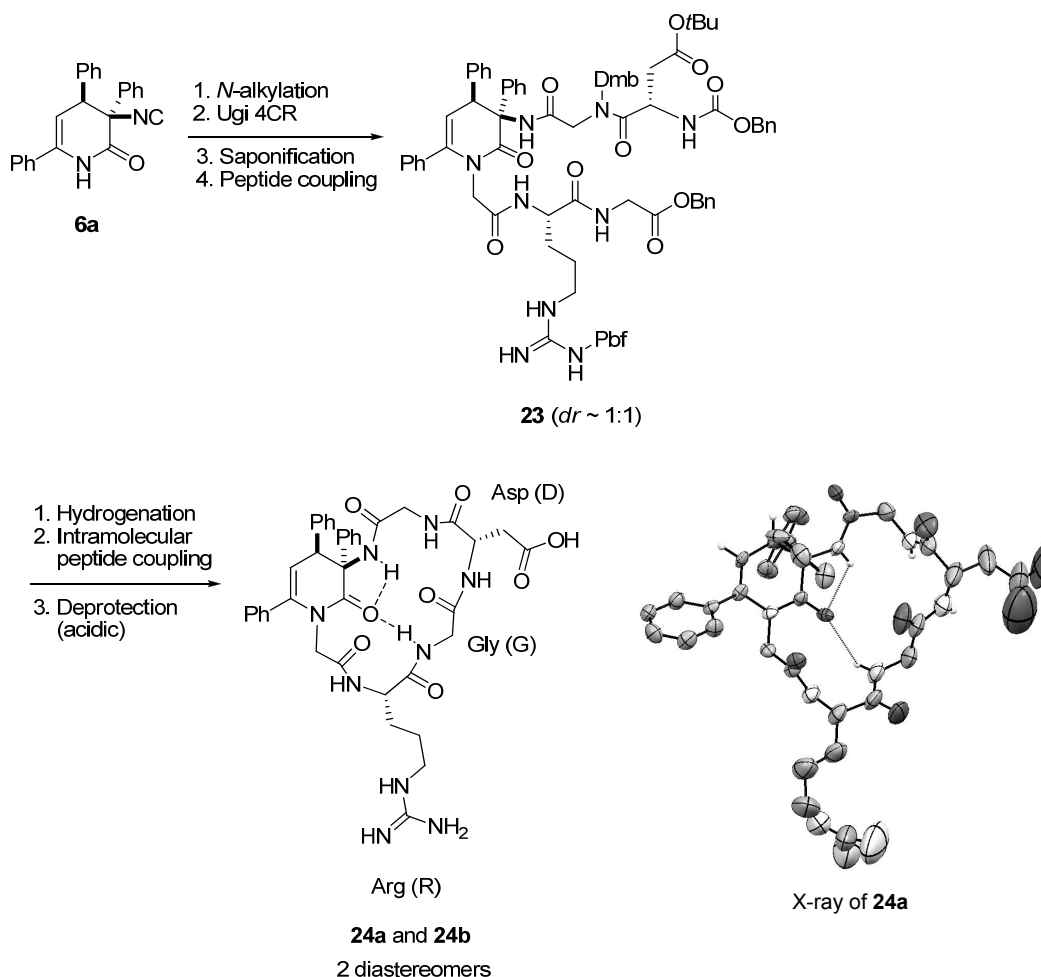
Scheme 5. Synthetic plan for the synthesis of constrained peptide **16a** possessing a methylated 3,4-DHP-2-one NH (NMe).

Although the 3,4-DHP-2-one scaffold was not able to induce a true β -turn conformation, it still induces a turn, showing an excellent preorganization for macrocyclization (Scheme 6). Our modular approach using two MCRs and an alkylation step allows unprecedented diversification of both the upper and lower peptide chains and the turn-inducing 3,4-DHP-2-one moiety, making a large range of 3,4-DHP-2-one containing cyclic peptides **22** available, after cyclization.



Scheme 6. The ability of 3,4-DHP-2-one containing peptides to be converted into constrained cyclic peptides.

In **Chapter 6** we applied this strategy for the synthesis of DHP-2-one containing cyclic RGD peptides **24a** and **24b**, which are potential $\alpha_{\text{IIb}}\beta_3$ or $\alpha_v\beta_3$ integrin inhibitors. These cyclic peptides are prepared *via* constrained peptide **23** by a hydrogenation, intramolecular peptide coupling (macrocyclization) and final acidic deprotection sequence (Scheme 7).



Scheme 7. Synthesis of 3,4-DHP-2-one containing cyclic RGD peptides **24a** and **24b**.

The conformations of **24a** and **24b** were evaluated by NMR analysis and X-ray diffraction (for one diastereomer), demonstrating that both diastereomers show rather similar conformations, with an extended RGD tripeptide conformation. This conformation suggests high activity and selectivity for the $\alpha_{\text{IIb}}\beta_3$ integrin, since this integrin proved selective for ligands adopting an extended RGD motif. However, inhibition studies showed *high* activities (in the nanomolar range) on *both* receptors ($\alpha_{\text{IIb}}\beta_3$ and $\alpha_v\beta_3$). The low selectivity needs improvement, which can generally be realized

by increasing the constrained nature of the peptides, by for example *N*-methylation of one or more amino acid residues or by reducing the ring size by means of removing one of the glycine units (but not the glycine of the RGD tripeptide).

In summary, this thesis demonstrates the high potential of the 1-azadiene, prepared *via* a 3CR, as a very versatile reaction intermediate for diversity-oriented synthesis using modular reaction sequences. Various heterocyclic scaffolds could be prepared by differentiating the fourth reaction component that reacts with the 1-azadiene intermediate *in situ*. In this work the 4CR to isonitrile-functionalized 3,4-dihydropyridin-2-one (3,4-DHP-2-one) was studied extensively. The 3,4-DHP-2-one scaffold proved to be a very useful scaffold for follow-up isonitrile-based chemistry, providing a way to access even more complex and diverse structures. This rather versatile scaffold furthermore realizes an excellent preorganization for macrocyclization (when incorporated in the middle of a peptide chain) which is demonstrated by the successful preparation of 3,4-DHP-2-one containing cyclic RGD peptides.